

EMERGING OPTIONS FOR PATIENTS WITH ATRIAL FIBRILLATION

Summary of Presentations from the Daiichi Sankyo Satellite Symposium, held at the Annual ESC Congress, Barcelona, Spain, on 31st August 2014

Co-Chairs

Jeffrey Weitz,¹ John Camm²

Speakers

Christian Ruff,³ Andreas Goette,⁴ Jack Ansell⁵

1. McMaster University, Hamilton, Ontario, Canada

2. St George's Healthcare NHS Trust, London, UK

3. Brigham & Women's Hospital, Boston, Massachusetts, USA

4. St Vincenz-Hospital, Paderborn, Germany

5. New York City, New York, USA

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MEETING SUMMARY

Dr Jeffrey Weitz chaired the symposium and welcomed Dr Christian Ruff, who discussed and summarised recent results from key trials of new oral anticoagulants (NOACs) in atrial fibrillation (AF) with a focus on edoxaban. Prof Andreas Goette then evaluated the current guidelines for the use of cardioversion in AF treatment and recent findings from NOAC trials. Dr Jack Ansell described the current management strategies for NOACs and the limitations therein, as well as novel reversal strategies for NOACs currently under development. Finally Prof John Camm, co-chair, summed up the use of NOACs as an alternative to warfarin in the prevention of stroke in patients with AF, and closed the meeting.

New Insights from ENGAGE AF-TIMI 48

Doctor Christian Ruff

Effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI

48)^{1,2} is the largest trial of a NOAC in AF, having enrolled 21,105 patients to one of three treatment strategies: higher-dose edoxaban (60 mg QD), lower-dose edoxaban (30 mg QD), or warfarin titrated to an international normalised ratio (INR) of 2.0–3.0.¹ The primary endpoint was stroke or systemic embolism, whilst the safety endpoint was

major bleeding, as per the International Society on Thrombosis and Haemostasis definition. An important aspect of the trial design included a 50% dose reduction of edoxaban (60-30 mg or 30-15 mg) for high-risk patients with clinical features anticipated to significantly increase drug exposure and risk of bleeding, defined as a creatinine clearance of 30-50 mL/min, weight \leq 60 kg, or receiving a strong P-glycoprotein (P-gp) inhibitor (verapamil, quinidine, or dronedarone).

This trial found that both edoxaban regimens had comparable efficacy to warfarin with regard to reducing stroke or systemic embolism (annualised rate of stroke or systemic embolism was 1.50% in the warfarin group, and 1.18% [$p < 0.001$ non-inferiority], and 1.61% [$p = 0.005$ non-inferiority] in the higher and lower-dose edoxaban arms, respectively). In addition, during the overall study period of 2.8 years, cardiovascular mortality was reduced by ~14-15%.² Importantly, both edoxaban regimens were associated with a significant reduction in major ($p < 0.001$), clinically-relevant non-major ($p < 0.001$), and minor bleeding ($p = 0.002$ for higher-dose and $p < 0.001$ for lower dose) compared with warfarin. However, although the rates of ischaemic stroke were comparable between higher-dose edoxaban and warfarin, a higher incidence was observed in patients receiving the lower-dose regimen.

Important insights gained from previous trials influenced the trial design for ENGAGE AF-TIMI 48;¹ for example, the safety issues that occurred when patients were transitioned from rivaroxaban to a vitamin K antagonist (VKA) upon completion of the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF) trial.³ 1 month post-trial, fewer than half of the rivaroxaban patients had INR values within the therapeutic range and subsequently had an increased risk of stroke compared with patients who were given warfarin throughout the trial.^{3,4} To minimise this effect during ENGAGE AF-TIMI 48,⁵ patients who were given a VKA had their INR checked frequently within the first 2 weeks and the dose was aggressively titrated to achieve a therapeutic range. In addition, treatment with a VKA was overlapped with a modified edoxaban dose. This strategy was successful in preventing the excess number of strokes seen previously, as ~85% and ~99% of patients were within the

therapeutic range 2 weeks and 1 month after transition, respectively.⁵

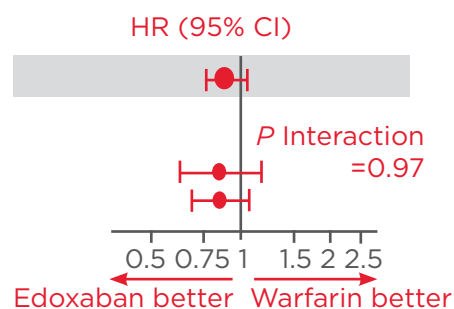
Another recent analysis from the ENGAGE AF-TIMI 48 study evaluated the mortality benefit of edoxaban compared with warfarin with regard to bleeding.⁶ Compared with the higher and lower-dose edoxaban groups, there were 66 and 102 excess deaths in the warfarin group. Of these, 39-45% were due to fatal bleeds and approximately 90% of the total excess deaths in the warfarin group were preceded by a major bleed. Thus, lower rates of fatal bleeding and major bleeding contributing to death accounted for over half the reduction in mortality observed in the edoxaban groups.

Prescription of anticoagulants is a balance of risks, with increased thrombosis or bleeding occurring if therapy is not adjusted correctly.⁷ Emerging data from the randomised evaluation of long-term anticoagulation therapy (RE-LY) study⁸ reported that higher dabigatran concentrations had a stronger correlation with bleeding events than stroke reduction. Investigators also observed that age impacted bleeding and stroke risk at a given dabigatran concentration. Due to the risks involved with anticoagulants, it would be beneficial if drug dosages could be modified according to patient risk factors. The ENGAGE AF-TIMI 48 trial⁹ subsequently assessed whether the dose of edoxaban could be adjusted using clinical factors alone, such as low body weight (\leq 60 kg), reduced renal function (creatinine clearance 30-50 mL/min), or concomitant treatment with a strong P-gp inhibitor. The study found that, compared with warfarin, the efficacy of edoxaban was maintained when the dose was reduced by half in high-risk populations (60-30 mg or 30-15 mg).² Interestingly, while efficacy was maintained, the risk of bleeding was further reduced, as shown in **Figure 1**. The reason for this appears to be the prevention of excess edoxaban exposure, resulting in lower anti-Xa activity and a better balance of risk for the patient.

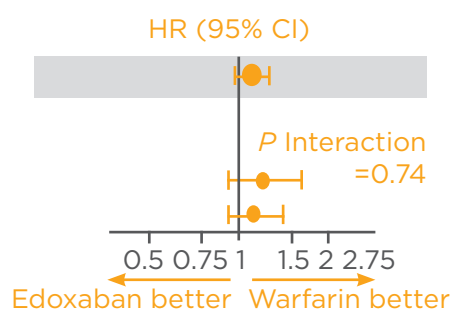
In conclusion, recent analyses of ENGAGE AF-TIMI 48 have demonstrated the comparable efficacy of edoxaban compared with warfarin, in conjunction with a lower incidence of bleeding events. Using the patient's clinical features to adjust the edoxaban dose was sufficient to prevent excess edoxaban levels and also optimise the balance between ischaemic and bleeding events, without having to measure prospectively the drug levels or anticoagulant activity.

A ENGAGE Dose Reduction: Preserved Efficacy

	Patients	Edoxaban 60/DR30 mg	Warfarin
All patients	21,105	1.57	1.80
Patient-specific dose reduction			
Yes	5,356	2.32	2.68
No	15,749	1.33	1.53

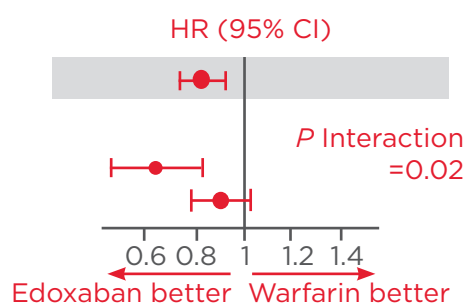


	Patients	Edoxaban 60/DR15 mg	Warfarin
All patients	14,070	2.04	1.80
Patient-specific dose reduction			
Yes	3,572	3.14	2.68
No	10,498	1.69	1.53



B ENGAGE Dose Reduction: Better Safety

	Patients	Edoxaban 60/DR30 mg	Warfarin
All patients	21,026	2.75	3.43
Patient-specific dose reduction			
Yes	5,330	3.05	4.85
No	15,696	2.66	3.02



	Patients	Edoxaban 60/DR15 mg	Warfarin
All patients	14,014	1.61	3.43
Patient-specific dose reduction			
Yes	3,550	1.50	4.85
No	10,464	1.65	3.02

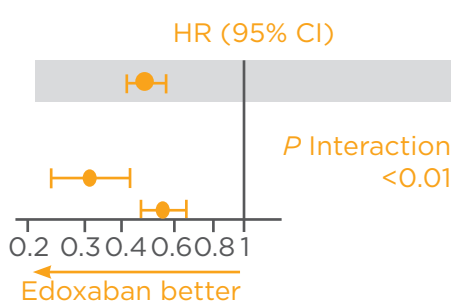


Figure 1: A) Hazard ratio (HR) of the primary efficacy outcome of stroke or systemic embolism with edoxaban versus warfarin; B) HR of the principal safety outcome of major bleeding with edoxaban versus warfarin.

CI: confidence interval.

Adapted from *Giugliano RP et al.*²

Future Direction of Anticoagulation Therapy

Professor Andreas Goette

Clot formation occurs in the presence of haemodynamic changes and endothelial injury

as described by Virchow's triad.¹⁰ Patients with AF have a higher likelihood of developing a clot and subsequent stroke than patients without AF.¹¹ Indeed, it has been shown that periods of AF as short as 5 minutes can increase the rate of stroke (Figure 2).¹²

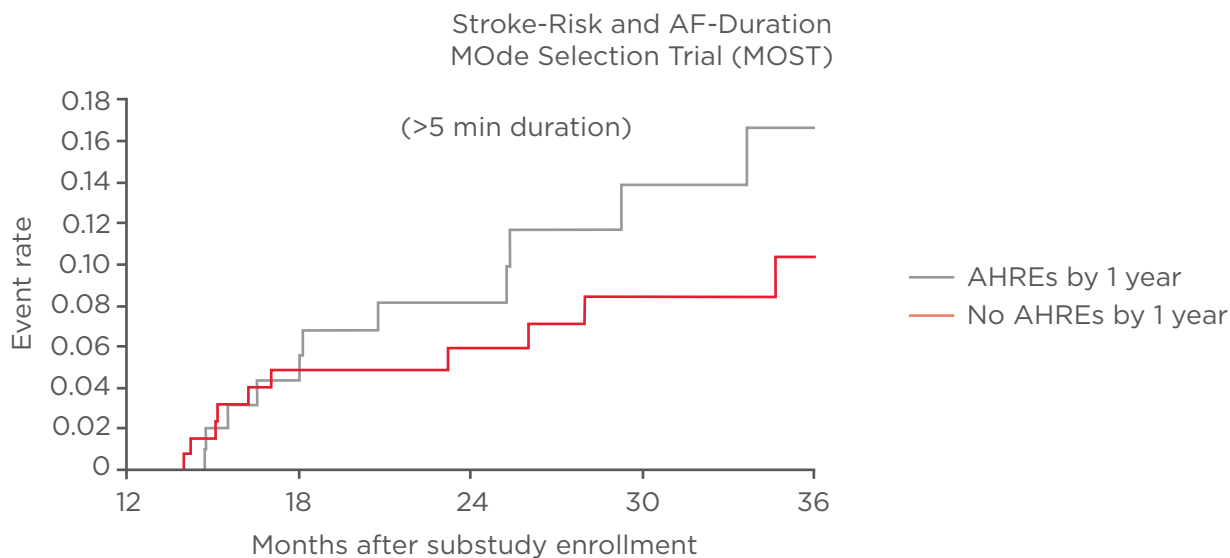


Figure 2: Kaplan-Meier plot of death or nonfatal stroke after 1 year of ancillary study follow-up in patients with AHREs versus those without AHREs.¹²

AF: atrial fibrillation; AHRE: atrial high rate episode.

Reprinted from Circulation, 107, Glotzer TV et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MDe Selection Trial (MOST), 1614-9 Copyright (2014), with permission from Wolters Kluwer Health.

Cardioversion is when an attempt is made to revert AF back to sinus rhythm, either by using drugs (pharmacologic cardioversion) or electric current (electric cardioversion). There is a risk of thromboembolism following cardioversion, so current guidelines recommend anticoagulant therapy prior to initiation of the procedure.¹³ VKAs are the main anticoagulants used for cardioversion because although NOACs are available for patients with AF, few data are available regarding their efficacy and safety in the cardioversion setting.

Sub-analyses of the key NOAC trials (RE-LY,¹⁴ ROCKET AF,³ and apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation [ARISTOTLE])¹⁵ confirmed no differences in the incidence of stroke between the NOACs and warfarin in patients undergoing cardioversion. However, the number of patients included in these sub-analyses was small and the studies were not sufficiently powered to fully elucidate the effect of NOACs during cardioversion.¹⁴ Therefore, prospective studies such as the XVERT trial¹⁶ are still required to establish efficacy.

The edoxaban versus warfarin in subjects undergoing cardioversion of atrial fibrillation (ENSURE in AF) study is the largest trial that will assess electrical cardioversion, recruiting at

approximately 300 sites and enrolling >2,000 patients across 20 countries (Daiichi Sankyo, data on file). Patients with AF lasting >48 hours within the past year, who are indicated for electrical cardioversion, will be primarily assessed for safety, and events such as major and non-major bleeds will be evaluated. Efficacy will also be monitored, although it may be limited due to the number of cardioversions required for statistical significance.

Patients may, or may not, undergo transoesophageal echocardiography (TEE) during the ENSURE in AF trial, after which warfarin (INR 2.0-3.0) or edoxaban (60 mg QD) will be given. Non-TEE guided approaches will have a pretreatment phase of 21 days so that full anticoagulant coverage is assured. While the standard edoxaban dose will be 60 mg, high-risk patients with a low body weight (≤ 60 kg), reduced creatinine clearance (15-50 mL/min), or concomitant use of a potent P-gp inhibitor (except amiodarone) will be given 30 mg edoxaban QD.

In summary, it is hoped that the ENSURE in AF trial, in conjunction with other prospective clinical trials, will provide robust data that can inform guidelines for patient care. Further prospective trials that assess cardioversion and catheter ablation are required in order to confirm the potential role of NOACs in all AF-associated procedures.

Table 1: Suggestions for reversal of target-specific oral anticoagulants.

Parameter	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
3-factor PCC	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Possible (activated)	Possible	Possible	Possible
Activated factor VIIa	No	No	No	No
FFP	No	No	No	No
Haemodialysis	Yes	No	No	No
Hemoperfusion with activated charcoal	Yes	Possible	Possible	N/A
Oral activated charcoal	Yes	Yes	Yes	N/A

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.
Updated after Kaatz et al.²⁴

Clinical Management of Treatment with NOACs

Doctor Jack Ansell

Until recently, VKAs were the only oral anticoagulant available for AF patients, and these required complex management. However, several NOACs have now been introduced that, while less complex than VKAs, may still require management. Although it is currently believed that the benefits of NOACs include a low requirement for management by physicians, there are a number of considerations to be assessed when prescribing these therapies.

Aspects to consider when prescribing the new anticoagulants include dosing strategies, possible drug interactions, peri-procedural management, adherence, monitoring, and follow-up.¹⁷ Available NOACs include dabigatran, rivaroxaban, and apixaban, while edoxaban is still under investigation. Each NOAC has both standard dosing and available modifications that can be given depending on patient risk factors, which can lead to complex requirements regarding which NOAC to use, and at which dose.¹⁸

Monitoring drug levels or drug effects during the course of anticoagulant treatment is not necessary, but even if it were desired, deciding the appropriate method and time-point for monitoring can be difficult. Compared with warfarin and other VKAs, NOACs produce sharp peaks and troughs of drug concentration and drug effect. Thus, one must consider that if the NOACs are to be monitored, should the blood samples be taken at the top,

middle, or bottom of the peaks and should repeat monitoring be done at the same time? Recent data have suggested that monitoring trough levels of dabigatran and maintaining an adjusted level may lead to less bleeding.⁸ However, despite the inherent limitations of monitoring, assessing drug level or drug effect under special circumstances, such as major bleeding and emergency situations, may be desired.

Further to this, available monitoring tests include prothrombin or thrombin time (TT) (presence of drug), chromogenic anti-factor Xa or dilute TT (amount of drug present), or the activated partial thromboplastin time (aPTT).¹⁹⁻²³ TT (dabigatran) is a widely available test but its high sensitivity to dabigatran can be a disadvantage. A normal TT essentially rules out any meaningful presence of dabigatran. Dilute TT tests, although not available everywhere, can provide a quantitative determination of dabigatran. For factor Xa inhibitors, the prothrombin time has variable sensitivity, and only certain reagents are suitable for dose-effect monitoring. The chromogenic anti-factor Xa assay provides a good quantitative measure, but it is not yet globally available.

On occasion, patients who are on anticoagulants require reversal strategies, such as when major bleeding events occur, or emergency procedures are necessary (Table 1).¹⁷ While it is important to note that only animal studies and anecdotal reports have been reported for NOAC reversal strategies so far,²⁴ haemodialysis can be used for dabigatran-related events, but may not be feasible under emergency situations, whilst fresh frozen

plasma (FFP) or activated factor VIIa should not be used for NOACs. Four factor prothrombin complex concentrates have been reported for Xa inhibitors and the activated form could be used for dabigatran-related major bleeding; however, the efficacy evidence is limited. Interestingly, a recent analysis compared the bleeding outcomes from five Phase III clinical trials involving dabigatran. While the dabigatran group received significantly more red cell transfusions and fewer FFP transfusions compared with the warfarin arms, there were no significant differences found regarding the number of patients who were hospitalised or died within 30 days.²⁵ Similar results were also found in the ROCKET AF trial.²⁶

Reversal therapies currently under investigation include an anti-dabigatran antibody (aDabi-Fab), which is in Phase III trials in healthy volunteers.²⁷ aDabi-Fab immediately reverses the effects of dabigatran for 24 hours and is renally eliminated. Promisingly, no detectable immunogenicity against the antibody was noted. Andexanet alfa is a modified, inactive, recombinant Xa reversal agent that binds to Xa inhibitors and prevents their binding to endogenous Xa in the coagulation cascade. It is currently under assessment in Phase III trials by Portola. This recombinant protein was found to be safe, effective, and well tolerated in a Phase I trial of 32 healthy volunteers, and has been shown to reverse anticoagulation within 5 minutes with the effects lasting for 3 hours.²⁸ Finally, aripazine (PER977) is a small molecule that binds by charge effects to NOACs. Phase I trial results reported the reversal of edoxaban effects

within ~10 minutes after an intravenous injection of aripazine, the effect of which lasted for 24 hours.^{29,30} The effect of aripazine was dose dependent and the drug was well tolerated.

In summary, although NOACs are more convenient than VKAs, active management is still required, and physicians should be aware of the multiple doses available per indication. Challenges of NOACs include the limited number of appropriate monitoring assays to measure the drug effect and the absence of a currently approved antidote, even though there is controversy over the necessity of such therapies.

Closing Remarks

Professor John Camm

Recent data indicate that NOACs provide a convenient alternative to warfarin in patients with AF, and may provide an alternative to warfarin for patients undergoing cardioversion, although more prospective data are required. However, while therapy with NOACs is simpler, some active management is still required under certain circumstances, although drug monitoring is rarely required. In particular, analyses of the ENGAGE AF-TIMI 48 trial have shown that modification of the edoxaban dose, based upon clinical characteristics, can prevent bleeding events in patients for whom the anticipated plasma concentration of edoxaban would be higher.

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